C

DECLARATION OF GREGORY A. BRENT, M.D.

In Support of the Citizen Petition of Abbott Laboratories
Docket No. 2003P-0387/CP1

Gregory A. Brent, M.D., under penalty of perjury, declares as follows:

1. I am a Professor of Medicine and Physiology at the University of California, Los Angeles, School of Medicine. I am also the Chief of the Endocrinology and Diabetes Division at the Veterans Affairs Greater Los Angeles Healthcare System ("VA Healthcare System"). Further, I am the Director of the Fellowship Program in Endocrinology, Metabolism, and Diabetes at the VA Healthcare System. Between 1995 and 2002, I was the Assistant Chief of Endocrinology at the West Los Angeles Veterans Affairs Medical Center. Between 1990 and 1995, I was an Assistant Professor of Medicine at Harvard Medical School and an Associate Physician at Brigham and Women's Hospital. Between 1987 and 1990, I was an Instructor in Medicine at Harvard Medical School.

2. I have been a member of the American Thyroid Association ("ATA") since 1988. Between 2000 and 2002, I served as a Director of the ATA, and I am currently the ATA's Secretary. I served on the ATA's Education Committee between 1992 and 1993, and on the ATA's Program Committee between 1993 and 1994. Since 1988, I have been a member of The Endocrine Society. I have been a member of the Editorial Board of the journal *Thyroid* since 1999, and also served at that position between 1995 and 1996. Between 1995 and 1997, I was the Associate Editor for *Thyroid*. I was the Scientific Editor for the *Journal of Endocrinology* between 1994 and 1996. Since 1986, I have served as a technical reviewer for molecular medicine and endocrinology for the *New England Journal of Medicine*. I have served

on the Editorial Board for *Endocrinology* since 2001, and on the Editorial Board for *Molecular Endocrinology* since 2002.

3. In 2003, I became a member of the Organizing Committee for the Centers for Disease Control and Prevention/ATA Conference, "The Impact of Maternal Thyroid Disease on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening." Also in 2003, I became a member of the Program Committee for the ATA/American Association of Clinical Endocrinologists Conference, "The Impact of Maternal Thyroid Status: Pregnancy, Fetal, and Childhood Development." I have published over 75 research articles, book chapters, and reviews related to thyroid hormone action and thyroid disease. Since 1997, I have given over 40 lectures and presentations relating to the thyroid gland. My curriculum vitae is attached at Tab 1.

4. My specialty in the field of endocrinology is thyroid diseases. My basic research looks at the mechanisms of thyroid hormone action and thyroid hormone regulation of neural development. In the clinical arena, I focus on hypothyroidism and the influence of women's thyroid status on pregnancy.

Hypothyroidism and Pregnancy

5. The thyroid gland is the first endocrine gland to appear in the development of a fetus. For the first 10 to 12 weeks of any pregnancy, the fetus is completely dependent upon the mother for the production of thyroid hormone. By the end of the first trimester, the fetus's thyroid gland begins to produce thyroid hormone on its own. The fetus remains dependent, however, on the mother to ingest adequate amounts of iodine throughout pregnancy, which is necessary to the fetus for making thyroid hormone.

6. The most common thyroid disorder occurring in women at the time of or during pregnancy is hypothyroidism. The most common cause of hypothyroidism in pregnant women is Hashimoto's thyroiditis, in which a patient's immune system attacks and destroys the thyroid gland. Other causes include inadequate treatment of a woman already known to have hypothyroidism, and overtreatment of a hyperthyroid woman with antithyroid medications.

7. For hypothyroid women, pregnancy carries many risks. Normal pregnancy requires increased thyroid hormone production from the thyroid gland. Thus, hypothyroid women who cannot compensate for this increased requirement are doubly at risk. Moreover, hypothyroidism can worsen already existing pregnancy symptoms such as morning sickness, fatigue, hair loss, and depression, and increase the risk of miscarriage, intrauterine growth retardation, pre-term delivery, and stillbirth.

8. Untreated or inadequately treated severe hypothyroidism in pregnant women also has been associated with maternal anemia (low red blood cell count), myopathy (muscle pain and weakness), congestive heart failure, pre-eclampsia (a pregnancy disorder that causes high blood pressure, persistent swelling, and large amounts of protein in the woman's urine), placental abnormalities, low birth weight infants, and postpartum hemorrhaging.

9. Women with subclinical (mild) hypothyroidism may have no symptoms, or may attribute any symptoms to their pregnancy because some of the symptoms of hypothyroidism (*e.g.*, fatigue and weight gain) are already quite common in pregnant women. This makes mild hypothyroidism especially difficult to detect.

10. Beginning in the second trimester, the major adverse obstetrical outcome associated with maternal hypothyroidism is an increased rate of fetal death. *See* Allan WC et al.,

Maternal Thyroid Deficiency and Pregnancy Complications: Implications for Popular Screening, J. Med. Screen. 7:127-130 (2000) (attached at Tab 2).

11. Untreated severe hypothyroidism in the woman can lead to impaired brain development in the fetus, especially when the maternal hypothyroidism is due to iodine deficiency. Further, studies have suggested that mild, asymptomatic, untreated hypothyroidism during pregnancy may still lead to mild brain development abnormalities in children. *See* Haddow JE et al., *Maternal Thyroid Deficiency During Pregnancy and Subsequent Neuropsychological Development of the Child*, N. Engl. J. Med. 341:549-555 (1999) (hereinafter "Haddow, *Maternal Thyroid Deficiency*") (attached at Tab 3).

12. Maternal hypothyroidism is diagnosed by a blood test that measures the serum concentration of thyroid stimulating hormone ("TSH"). Typically, when the thyroid gland is not producing enough thyroxine ("T4"), the pituitary gland senses this and secretes TSH, which signals the thyroid gland to produce more T4. But in women with hypothyroidism, the thyroid gland cannot produce enough T4 in response to the pituitary gland's signal – and, in response, the pituitary gland secretes even more TSH. Thus, hypothyroidism is diagnosed by detection of an elevated serum TSH level.

13. Just as with the treatment for men and non-pregnant women, hypothyroidism during pregnancy is treated with thyroid hormone replacement in the form of synthetic levothyroxine, such as Synthroid®. Thyroid hormone replacement therapy, when regularly monitored, is completely safe to take during pregnancy.

14. The amount of additional levothyroxine required depends on the nature of the underlying thyroid disease, the level of pre-pregnancy levothyroxine replacement, and the

stage of pregnancy. Because pregnancy requires increased thyroid hormone production, 50 to 70% of pregnant women already being treated for hypothyroidism require an increase in their levothyroxine dose, usually in the range of 25 to 50%. Women with hypothyroidism require frequent monitoring of thyroid function throughout pregnancy, primarily with serum TSH level tests. Mandel SJ et al., *Increased Need for Thyroxine During Pregnancy in Women With Primary Hypothyroidism*, N. Engl. J. Med. 323:91-96 (1990) (attached at Tab 4).

15. A number of sources have identified the importance of maintaining normal maternal thyroid status during pregnancy to reduce maternal and fetal complications. *See, e.g.*, Gharib H et al., *Subclinical Hypothyroidism During Pregnancy: Position Statement from the American Association of Endocrinologists*, Endocrine Practice 5:367-368 (1999) (attached at Tab 5). Indeed, studies have shown that the complications for a woman and her developing fetus are not a consequence of the underlying disease producing hypothyroidism, but of the adequacy of thyroid hormone replacement. *See, e.g.*, Abalovich M et al., *Overt and Subclinical Hypothyroidism Complicating Pregnancy*, Thyroid, 12:63-68 (2002) (hereinafter "Abalovich, *Overt and Subclinical Hypothyroidism*") (attached at Tab 6). Thus, hypothyroid women who are appropriately treated with levothyroxine and have normal TSH levels throughout pregnancy do not have any more complications of pregnancy than euthyroid women (*i.e.*, women with normal TSH levels). Given the profound impact of pre-term delivery, *in utero* death, and impaired intellectual development in children, adequate treatment of thyroid disease in pregnancy must be given a very high priority.

The Need for Precise Dosing

16. As noted earlier, the maintenance of normal maternal thyroid status during pregnancy to reduce maternal and fetal complications is critical. Numerous studies demonstrate

that even modest elevations in serum TSH, indicating inadequate levothyroxine replacement during pregnancy, can have significant and permanent consequences on a woman and her fetus. *See* Haddow, *Maternal Thyroid Deficiency*; Abalovich, *Overt and Subclinical Hypothyroidism*.

17. In my clinical experience, modest elevations in the serum TSH levels of a pregnant woman can be caused by changes in levothyroxine dosage of as little as 9%. This means that exposure to two manufacturers' levothyroxine products, which differ by this amount, can likewise have significant consequences for a pregnant woman and her developing fetus. Such products, in my view, cannot safely be substituted for each other and cannot be considered to be therapeutically equivalent.

Dated: Los Angeles, California
February 5, 2004

Gregory A. Brent, M.D.